

1                   THERAPEUTIC COMPOSITION AND DELIVERY SYSTEM FOR  
2                   ADMINISTERING DRUG  
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4                   CROSS-REFERENCE TO RELATED APPLICATION  
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6                   This application claims the benefits of provisional application U.S.  
7                   Serial No. 60/060,242 filed September 29, 1997 under 35 U.S.C. §119 (e).  
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9                   FIELD OF THE INVENTION  
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11                  This invention pertains to both a novel therapeutic composition and to  
12                  a novel delivery system. More particularly, the invention relates to (1) a  
13                  therapeutic composition comprising a polyitol and a drug for administering to  
14                  a patient, and, to (2) a delivery system comprising the therapeutic  
15                  composition for delivering the therapeutic composition to a patient. The  
16                  invention concerns also a method for administering a drug to a patient in need  
17                  of therapy.

18

19                   BACKGROUND OF THE INVENTION  
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21                  Delivery systems for administering a therapeutic composition to a  
22                  patient in need of therapy are known to the medical and pharmaceutical arts.  
23                  For example, in U. S. Patent Nos. 3,845,770 issued to Theeuwes and  
24                  Higuchi, and in U. S. Patent No. 3,916,899 issued to the same patentees, a  
25                  device is disclosed comprising a wall that surrounds a compartment  
26                  containing a beneficial agent for delivery to a patient. The wall of the device  
27                  is permeable to the passage of fluid and it comprises a passageway that is  
28                  preformed or formed during use of the device for delivering the beneficial  
29                  agent to the patient. The devices of these patents release the beneficial  
30                  agent by fluid being imbibed through the wall into the device at a rate

1 determined by the permeability of the wall and the osmotic pressure gradient  
2 across the wall. The fluid imbibed into the device mixes with the beneficial  
3 agent to form an aqueous media comprising the beneficial agent that is  
4 dispensed through the passageway from the device over time. The devices  
5 of these patents are extraordinarily effective for delivering a beneficial agent  
6 that is soluble and stable in aqueous and biological fluids and exhibit an  
7 osmotic pressure gradient across the wall against an external fluid. The  
8 devices of these patents are effective also for delivering a beneficial agent  
9 that is mixed with an osmotically effective solute soluble in fluid that exhibits  
10 an osmotic pressure gradient across the wall against an aqueous fluid.

11 A further advancement in the delivery art for dispensing a stable  
12 formulation is disclosed in U.S. Patent No. 3,995,632 issued to Nakano,  
13 Higuchi, and Hussain. The dispenser disclosed in this patent dispenses a  
14 stable composition that absorbs heat and forms a dispensable melt. The melt  
15 is dispensed by a solution of magnesium sulfate increasing in volume and  
16 occupying the space originally occupied by the melt.

17 A quantum improvement in osmotic devices was presented to the  
18 pharmaceutical and medical dispensing arts by inventor Theeuwes in U.S.  
19 Patent Nos. 4,111,202; 4,111,203; and 4,203,439. In these patents the  
20 delivery kinetics of the devices were enhanced for delivering a beneficial  
21 agent with different degrees of solubility in an aqueous-type fluid. The  
22 kinetics were improved by manufacturing the devices with a beneficial agent  
23 compartment separated by a film from an osmotic compartment. The devices  
24 deliver the beneficial agent by fluid being imbibed through the wall into the  
25 osmotic compartment to fill the compartment with fluid that acts as a driving  
26 force and thereby causes the film to move. The film moves against the  
27 beneficial agent compartment and the driving forces pushes the beneficial  
28 agent through a passageway from the device.

29 A pioneering advancement in osmotic delivery devices was made by  
30 Cortese and Theeuwes in U.S. Patent No. 4,327,725 and by Wong, Barclay,

1 Deters, and Theeuwes in U.S. Patent No. 4,612,008. The devices disclosed  
2 in these patents comprise a semipermeable wall that surrounds a  
3 compartment. The compartment contains a beneficial agent formulation and  
4 a hydrogel. These devices operate by imbibing fluids into the compartment,  
5 wherein it contacts the beneficial agent formulation and forms a dispensable  
6 formulation, and wherein the imbibed fluid contacts the hydrogel causing it to  
7 expand and push the dispensable aqueous formulation from the device.

8 The delivery devices described in the above patents operate  
9 successfully for their intended use, and they can deliver many beneficial  
10 agents for their intended effects. Now, it has been observed their use can be  
11 limited because the devices lack the necessary elements to deliver beneficial  
12 agents that are sensitive or insensitive to fluids. The prior art are sought to solve  
13 these limitation by using hydrogel swelling agents, to carry the beneficial  
14 agent from the device. These swelling agents, however, when contacted by  
15 an aqueous fluid often developed a swelling pressure so great they caused  
16 the wall of the device to rupture. Or, the swollen agent can entrap in its  
17 structure the beneficial agent and thereby make the beneficial agent  
18 unavailable for therapy.

19 It will be appreciated by those versed in the drug-dispensing art, in  
20 view of the above presentation, that a pressing need exists for a novel  
21 therapeutic composition and a delivery system essentially-free of the  
22 limitations associated with the prior art. It will be appreciated also, that if a  
23 therapeutic composition and a delivery system are provided essentially-free of  
24 a drug-swelling agent formulation, such a novel therapeutic composition and  
25 delivery system would have a positive value, and represent an advancement  
26 in the dispensing arts. Likewise, it will be self-evident, that a novel  
27 composition and delivery system, will have practical applications in the fields  
28 of human and veterinary medicine, and in the management of health.

## OBJECTS OF THE INVENTION

3 Accordingly, in view of the above presentation it is an immediate object  
4 of this invention to provide a therapeutic composition and a dosage form,  
5 which substantially overcome the deficiencies and omissions associated with  
6 the prior art.

7 Another object of the present invention is to provide a therapeutic  
8 composition that can administer a beneficial drug for the management of  
9 health.

10 Another object of the invention is to provide a therapeutic composition  
11 that can administer an aqueous insoluble to an aqueous soluble drug in an  
12 effective dose for a therapeutic benefit.

13 Another object of the invention is to provide a therapeutic composition  
14 for administering a dose of drug to a patient for establishing a drug level in the  
15 blood of the patient as a function of the dose administered by the therapeutic  
16 composition

17 Another object of the present invention is to provide a dosage form for  
18 administering a drug in a controlled-continuous-release rate to a patient for  
19 establishing an essentially-constant drug level in the blood as a function of a  
20 prolonged-release dosage form.

21 Another object of the present invention is to provide a dosage form that  
22 reduces and/or eliminates the unwanted influences of a gastrointestinal  
23 environment on the delivery of a drug in the gastrointestinal tract.

24 Another object of the present invention is to provide an improvement in  
25 a dosage form by administering a drug to a patient in need of drug therapy,  
26 wherein the improvement comprises delivering the drug from a dosage form  
27 in a continuous-release dose for predictable and improved therapy.

28 Another object of the present invention is to provide a method for  
29 administering a drug by orally administering the drug in a known dose per unit  
30 time over an extended time to a patient in need of therapy.

1           Another object of the invention is to provide drug delivery devices  
2   powered by osmotic energy for the controlled delivery of a therapeutically  
3   acceptable drug to an aqueous-biological environment of use.

4           These and other objects of this invention will be readily apparent to  
5   those skilled in the relevant are enabled by the disclosure herein.

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7           **BRIEF DESCRIPTION OF THE DRAWINGS**

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9           In the drawing figures, which are not drawn to scale, but are set forth to  
10   illustrate various embodiments of the invention, the drawing figures are as  
11   follows:

12           Drawing Figure 1 as a general view of a dosage form, designed and  
13   shaped for oral administration for delivering a drug at a continuous-release  
14   rate over an extended time to a patient in need of therapy;

15           Drawing Figure 2 is an opened view of the dosage form of Figure 1,  
16   illustrating a dosage form comprising a single pharmaceutical composition  
17   comprising a drug and a pharmaceutically acceptable polyitol for delivering  
18   the pharmaceutical composition from the dosage form to a patient;

19           Drawing Figure 3 is an opened view of drawing Figure 1 illustrating a  
20   dosage form comprising a pharmaceutical composition comprising a drug and  
21   a polyitol and a displacement composition for pushing the pharmaceutical  
22   composition from the dosage form;

23           Drawing Figure 4 illustrates the cumulative dose of drug delivery by a  
24   dosage form of this invention over time.

25           In the drawings, and in the specification, like parts on related figures  
26   are identified by like numbers. The terms appearing earlier in the  
27   specification and in the description of the drawings as well as embodiments  
28   thereof are further described in the specification.

29

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawing figures in detail, which drawing figures are examples of compositions and dosage forms provided by the invention, and which examples are not to be construed as limiting, one example of a dosage form comprising a composition is seen in drawing Figure 1. In drawing Figure 1, a dosage form 10 is seen comprising a body member 11 comprising a wall 12, this surrounds and forms an internal area, not visible in drawing Figure 1. Drawing Figure 1 comprises at least one exit 13 that connects the exterior of dosage form 10 with the interior of dosage form 10. The dosage form 10 of drawing Figure 1 illustrates a controlled-release dosage form that delivers a drug over an extended time. The dosage form comprising the controlled-release properties provided by this invention is successful at maintaining therapeutic drug levels in blood or in body tissue. The terms blood and body tissue refer to human patients, zoo and farm animals. The dosage form provided by this invention makes available to the practice of medicine continuous-release, extended-release therapy. The phrase extended release embraces sustained release and prolonged release over up to a single day of therapy. The extended, prolonged and sustained release denotes a duration of drug delivery time over that achieved by conventional drug delivery forms such as tablets and capsules.

In drawing Figure 2, dosage form 10 of drawing Figure 1 is seen in opened-section. In drawing Figure 2, dosage form 10, compress a body 11, a wall 12 that surrounds and defines an internal compartment 14. Internal compartment 14 communicates through exit 13 with the exterior of dosage form 10. Wall 12 of dosage form 10 comprises totally, or in as least a part a semipermeable composition. The semipermeable composition is permeable to the passage of an aqueous fluid, or a biological fluid present in the gastrointestinal tract, and it is impermeable to the passage of drug. Wall 12 is nontoxic and it maintains its physical and chemical integrity during the

1 dispensing time of a drug. The phrase, maintains its physical and chemical  
2 integrity means wall 12 does not lose its structure and it does not undergo a  
3 major change during the dispensing of a drug.

4 Wall 12 comprises a composition that does not adversely affect an  
5 animal, a human, or components of the dosage form. Compositions for  
6 forming wall 12 are, in one embodiments, comprised a member selected from  
7 the group consisting a cellulose ester polymer, a cellulose ether polymer and  
8 a cellulose ester-ether polymer. These cellulosic polymers have a degree of  
9 substitution, DS on the anhydroglucoside unit, from greater than 0 up to 3  
10 inclusive. By "degree of substitution" is meant the average number of  
11 hydroxyl groups originally present on the anhydroglucoside unit comprising the  
12 cellulose polymer that are replaced by a substituting group. Representative  
13 wall 12 polymers comprise a member selected from the group consisting of  
14 cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate,  
15 cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose  
16 alkylates, mono-, and di- and tricellulose alkylates. Exemplary polymers  
17 include cellulose acetate having a DS of up to 1 and an acetyl content of up  
18 to 31%; cellulose acetate having a DS of 1 to 2 and any acetyl content of 21  
19 to 35%; cellulose acetate having a DS of 2 to 3 and an acetyl content of 35 to  
20 44.8%; and the like. More specific cellulosic polymers comprise cellulose  
21 propionate having a DS of 1.8, a propyl content of 39.2 to 45% and a hydroxyl  
22 content of 2.8 to 5.4; cellulose acetate butyrate having a DS of 1.8, an acetyl  
23 content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate  
24 butyrate having a acetyl content of 2 to 29%, a butyryl content of 17% to 53%  
25 and a hydroxyl content of 0.5 to 4.7; cellulose triacylates having a DS of 2.9  
26 to 3, such as cellulose trivalerate, cellulose trilauroate, cellulose tripalmitate,  
27 cellulose trisuccinate and cellulose trioctanoate; celluloses diacylate having a  
28 DS of 2.2 to 2.6, such as cellulose disuccinate, cellulose dipalmitate, cellulose  
29 dioctanoate, cellulose dipentanoate, co-esters of cellulose, such as cellulose  
30 acetate butyrate, and cellulose acetate propionate.

1        Additional semipermeable polymers comprise acetaldehyde  
2        dimethylcellulose acetate; cellulose acetate ethylcarbamate; cellulose acetate  
3        methylcarbamate; cellulose diacetate propylcarbamate; cellulose acetate  
4        diethylaminoacetate; semipermeable polyamide; semipermeable  
5        polyurethane; semipermeable sulfonated polystyrene; semipermeable  
6        crosslinked selective polymer formed by the coprecipitation of a polyanion  
7        and polycation, as disclosed in U.S. Patents Nos. 3,173,876; 3,276,586;  
8        3,541,005; 3,541,006 and 3,546,876; semipermeable polymers as disclosed  
9        by Loeb and Sourirajan in U. S. Patent No. 3,133, 132; semipermeable, lightly  
10       crosslinked polystyrenes; semipermeable crosslinked poly (sodium styrene  
11       sulfonate); semipermeable cross-linked poly (vinylbenzyltrimethyl ammonium  
12       chloride); and semipermeable polymers possessing a fluid permeability of 2.5  
13        $\times 10^{-8}$  to 5  $\times 10^{-2}$  (cm<sup>2</sup>/hr•atm), expressed per atmosphere of hydrostatic or  
14       osmotic pressure difference across the semipermeable wall. The polymers  
15       are known to the polymer art in U.S. Patents Nos. 3,845,770; 3,916,899 and  
16       4,160,020; and in Handbook of Common Polymers, Scott, J. R. and W. J.  
17       Roff, 1971, CRC Press, Cleveland OH.

18       In drawing Figure 2, internal compartment 14 comprises a single,  
19       homogenous composition. The composition comprises 0.5 wt % to 65 wt %  
20       of a drug, and 60 wt % to 99.5 wt % of a polyitol. The composition can  
21       comprise 0 wt % to 5 wt % of a lubricant, 0 wt % to 5 wt % of a binder, and 0  
22       wt % to 3 wt % of a colorant. The total weight of all the compositional  
23       ingredients equals 100 wt %.

24       Dosage form 10 comprises in compartment 14 a therapeutic agent 15,  
25       represented by dots. The term therapeutic agent as used herein included  
26       medicines or drugs, nutrients, vitamins, food supplements, and other  
27       beneficial agents that provide a therapeutic or a benefit to animals, including  
28       a warm-blooded animal, humans, farm animals, and zoo animals.  
29       Representative of therapeutic agent 15 comprise vancomycin, phentolamine,  
30       valoxifene, cyclosporin, lisinopril, ondansetron, fluvoxamine, captoril,

1 enalapril, amisulpride, imipramine, carbamazepine, famciclovir, clomipramine,  
2 penciclovir, pergolide, mesalazine, enitabas, talviraline, clozapine, nevirapine,  
3 zidovudine, ganciclovir alendronic, imiquimod, naratriptan, sparfloxacin,  
4 lamivudine, zidovudine, omeprazole, aiclovir, valaceclovir, oxcarbazepine,  
5 ganciclovir, amfebutamone, cidofovir, doxazosin, ebastine, formoterol,  
6 moexipril, penciclovir, sertraline, spirapril, fenfluramine, dexfenfluramine,  
7 phentermine, fenphen, oxybutynin, felodipene, metoprolol, saquinavir,  
8 ritonavir, indinavir, and nelfinavir.

9 The therapeutic composition in compartment 14 comprises polyitol 16,  
10 represented by dashes. The polyitol comprises two or more HCOH groups.  
11 The polyitols are represented by a member selected from the group  
12 consisting of tetritols, pentitols, hexitols, heptitols, and octitols. The tetritols  
13 comprise a member selected from the group consisting of erythritol, meso-  
14 erythritol, D-threitol, and L-threitol; the pentitols comprise a member selected  
15 from the group consisting of ribitol, D-arabinitol, L-arabinitol, xylitol, meso-  
16 ribitol, lyritol, and meso-xylitol; the hexitols are represented by a member  
17 selected from the group consisting of allitol, glucitol, mannitol, dulcitol, iditol,  
18 altritol, glactitol, talitol, maltitol and lactitol; the heptitols and octitols are  
19 represented by heptitol, and octitol.

20 The therapeutic composition comprises a lubricant 17 used during  
21 manufacture of the composition to prevent or reduce adhesion of the  
22 composition to the surface of dies and punches. The lubricants comprise  
23 calcium stearate, zinc stearate, magnesium stearate, magnesium oleate,  
24 calcium palmitate, sodium suberate, potassium laurate, stearic acid, salts of  
25 fatty acids, salts of alicyclic acids, salts of aromatic acids, oleic acid, palmitic  
26 acid, a mixture of a salt of a fatty, alicyclic or aromatic acid. The therapeutic  
27 composition can comprise a binder 18, represented by slanted dashes. The  
28 binder imparts cohesive qualities to the composition. Representative of  
29 materials for this invention useful as binders comprise a member selected  
30 from the group consisting of starch, gelatin, molasses, polyvinylpyrrolidone,

1       methylcellulose and hydroxypropylmethylcellulose. The binder can be used  
2       as a solution, or in a dry form to prepare the therapeutic composition.

3       Drawing Figure 3 depicts dosage form 10 comprising the therapeutic  
4       composition and a displacement composition for pushing the therapeutic  
5       composition from dosage form 10. The therapeutic composition comprises  
6       drug 15, polyitol 16, lubricant 17 and binder 18. The therapeutic composition  
7       is initially in contact with a displacement composition. The therapeutic  
8       composition can be classified a layer 19 and the displacement composition  
9       can be classified as layer 20, which layers 19 and 20 produce a bilayer core.  
10      The displacement composition comprises an osmopolymer 21 comprising 25  
11      mg to 250 mg of a member selected from the group consisting of polyalkylene  
12      oxide of 1,500,000 to 8,500,000 weight-average molecular weight and  
13      carboxymethylcellulose of 175,000 to 6,000,000 weight average molecular  
14      weight. More specifically the polyalkylene oxide comprise polyethylene oxide  
15      and polypropylene oxide and the carboxymethylcellulose comprises alkali  
16      carboxymethylcellulose, sodium carboxymethylcellulose, and potassium  
17      carboxymethylcellulose. The displacement composition can comprise 0.5 mg  
18      to 50 mg of an osmagent 22. The osmagent 22 imbibes fluid into the  
19      displacement composition for cooperating with osmopolymer 21 for displacing  
20      the therapeutic composition from the dosage form. The osmagent 22  
21      comprise a member selected from the group consisting of sodium chloride,  
22      potassium chloride, lithium chloride, potassium acid phosphate, tartaric acid,  
23      citric acid, magnesium sulfate, magnesium chloride, urea, and a mixture of  
24      sodium chloride and urea. The displacement composition can comprise a  
25      colorant 23. The colorant 23 makes the dosage form more esthetic in  
26      appearance and it serves to identify the dosage form during manufacture and  
27      therapy. The colorants, comprise 0.00 to 4.5 mg, represented by FD &C Red  
28      No. 3; FD&C Red No 40; FD&C Yellow No. 5; FD&C Yellow No. 6; FD&C  
29      Blue No. 1; FD&C Blue No. 2; FD&C Green No. 3; and iron oxides including  
30      red ferric oxide and yellow ferric oxide. The displacement composition

1 comprises 0.00 to 5 mg of a lubricant 24 selected from the group consisting of  
2 calcium stearate, magnesium stearate, zinc stearate, magnesium oleate,  
3 calcium palmitate, sodium laurate, stearic acid, oleic acid, palmitic acid, and a  
4 mixture of magnesium stearate and stearic acid.

5 The drawing figures provided above dictate the invention makes  
6 available a drug composition, a bilayer comprising a drug composition and a  
7 displacement layer, and a dosage form for administering a sustained release  
8 of drug. The invention provides for the drug composition and the  
9 displacement composition in a bilayer structure to be surrounded by a wall  
10 comprising a semipermeable composition, with a exit for delivering the drug to  
11 a human patient in need of therapy.

12 The expression "passageway" as used herein comprises means and  
13 methods suitable for the metered release of the therapeutic drug from the  
14 compartment of the dosage form. The exit means comprises at least one  
15 passageway including orifice, bore, aperture, pore, porous element, hollow  
16 fiber, capillary tube, porous overlay, or porous element that provides for the  
17 osmotic controlled release of drug. The passageway includes a material that  
18 erodes or is leached from the wall in a fluid environment of use to produce a  
19 dimensional passageway. Representative materials suitable for forming a  
20 passageway, or a multiplicity of passageways comprise a leachable  
21 poly(glycolic) acid or poly(lactic) acid polymer in the wall, a gelatinous  
22 filament, poly(vinyl alcohol), leachable polysaccharides, salts and oxides. A  
23 pore passageway, or more than one pore passageway, can be formed by  
24 leaching a leachable compound, such as sorbitol, from the wall. The  
25 passageway possesses controlled-release dimensions, such as round,  
26 triangular, square and elliptical for the metered release of drug from the  
27 dosage form. The dosage form can be constructed with one or more  
28 passageways in spaced apart relationship on a single surface or on more  
29 than one surface of the wall. The expression "fluid environment" denotes an  
30 aqueous or biological fluid as a human patient, including the gastrointestinal

1 tract. Passageways and equipment for forming passageways are disclosed in  
2 U. S. Patents Nos. 3,845,770; 3,916,899; 4,063,064; 4,088,864 and  
3 4,816,263. Passageways formed by leaching are disclosed in U. S. Patent  
4 Nos. 4,200,098 and 4,285,987.

5

6 **DESCRIPTION FOR MANUFACTURING THE COMPOSITION**  
7 **AND DOSAGE FORM OF THE INVENTION**

8

9 The wall of the dosage form can be formed by using the air suspension  
10 procedure. This procedure consists in suspending and tumbling the  
11 composition or the layers in a current of air and wall-forming composition until  
12 a wall is applied to the drug forming compartment. The air suspension  
13 procedure is well suited for independently forming the wall. The air  
14 suspension procedure is described in U. S. Patent No. 2,799,241; J. Am.  
15 Pharm. Assoc., Vol. 48, pp. 451-459 (1959); and ibid., Vol. 49, pp. 82-84  
16 (1960). The wall can be formed with a wall-forming composition in a Wurster®  
17 air suspension coater using an organic solvent, such as acetone-water  
18 cosolvent 90:10 (wt;wt) with 2.5 wt% to 7 wt% polymer solids. An Aeromatic®  
19 air suspension coater using, for example, a methylene dichloride methanol  
20 cosolvent comprising 87:13 (v:v) can be used for applying the wall. Other  
21 wall-forming techniques, such as pan coating, can be used for providing the  
22 dosage form. In the pan coating system wall forming compositions are  
23 deposited by successive spraying of the composition or the bilayered  
24 arrangement, accompanied by tumbling in a rotating pan. A larger volume of  
25 cosolvent can be used to reduce the concentration of polymer solids to  
26 produce a thinner wall. Finally, the wall of the coated compartments are laser  
27 or mechanically drilled, and then dried in a forced air or humidity over for 1 to  
28 3 days or longer to free the solvent. Generally, the walls formed by these  
29 techniques have a thickness of 2 to 20 mils (0.051 to 0.510 mm) with a  
30 preferred thickness of 2 to 7 mils (0.076 to 0.180 mm).

1        The dosage form of the invention in another embodiment is  
2 manufactured by standard manufacturing techniques. For example, in one  
3 manufacture the beneficial drug and other ingredients comprising a  
4 therapeutic composition or comprising the first layer facing the exit means are  
5 blended, or the ingredients are blended then pressed, into a solid layer. The  
6 drug and other ingredients can be blended with a solvent and formed into a  
7 solid or semisolid formed by conventional methods such as ball-milling,  
8 calendering, stirring or roll-milling and then pressed into a selected shape.  
9 The drug layer posses dimensions that correspond to the internal dimensions  
10 of the area the drug layer is to occupy in the dosage from. Next, the drug  
11 layer is placed in contact with the displacement layer. The layering of the  
12 drug layer and the displacement layer can be fabricated by conventional  
13 press-layering techniques. The bilayers possess dimensions corresponding  
14 to the dimensions of the internal compartment or the dosage form. Finally,  
15 the two-layer compartment forming members are surrounded and coated with  
16 an outer wall. A passageway is laser drilled or mechanically drilled through  
17 the wall to contact the drug layer, with the dosage form optically oriented  
18 automatically by the laser equipment for forming the passageway on the  
19 preselected drug surface.

20        In another manufacture, the dosage from is manufactured by the wet  
21 granulation technique. In the wet granulation technique the drug and the  
22 ingredients comprising the first layer are blended using an organic or  
23 inorganic solvent, such as isopropyl alcohol-methylene dichloride 80:20 (v:v)  
24 as the granulation fluid. Other granulating fluid, such as water, isopropyl  
25 alcohol, or 100% denatured alcohol can be used for this purpose. The  
26 ingredients forming the first layer are individually passed through a 40 mesh  
27 or like screen and then thoroughly blended in a mixer. Next, other ingredients  
28 comprising the first layer are dissolved in a portion of the granulation fluid,  
29 such as the cosolvent described above. Then, the latter prepared wet blend  
30 is slowly added to the drug blend with continual mixing in the blender. The

1 granulating fluid is added until a wet blend mass is produced, which wet mass  
2 is then forced through a 20 mesh or like screen onto oven trays. The blend is  
3 dried for 18 to 24 hours at 25°C to 40°C. The dry granules are then screened  
4 with a 16 mesh or like screen. Next, a lubricant is passed through a 60 mesh  
5 or like screen and added to the dry screened granule blend. The granulation  
6 is put into milling jars and mixed on a jar mill for 2 to 10 minutes. The first  
7 and second layered compositions are pressed into a layered tablet, for  
8 example, in a Manesty® layer press.

9 Another manufacturing process that can be used for providing the drug  
10 and displacement compositions comprise blending their powdered ingredients  
11 in a fluid bed granulator. After the powdered ingredients are dry blended in  
12 the granulator, a granulating fluid, for example, poly(vinylpyrrolidone) in a  
13 solvent, such as in water, is sprayed onto the respective powders. The  
14 coated powders are then dried in a granulator. This process coats the  
15 ingredients present therein while spraying the granulating fluid. After the  
16 granules are dried, a lubricant, such as stearic acid or magnesium stearate, is  
17 blended as above into the mixture. The granules are then pressed in the  
18 manner described above. In another embodiment, when the fluid be  
19 granulating process is used to manufacture the displacement layer, an  
20 antioxidant present in the polyalkylene oxide can be removed during the  
21 processing step. If antioxidant is desired, it can be added to the displacement  
22 layer, this can be accomplished during the fluid bed granulation described  
23 above.

24 The dosage form of this invention is manufactured in another  
25 embodiment by mixing a drug with composition-forming ingredients and  
26 pressing the composition into a solid layer possessing dimensions that  
27 correspond to the internal dimensions of the compartment space adjacent to  
28 a passageway. In another embodiment, the drug and other drug composition  
29 forming ingredients and a solvent are mixed into a solid, or semi-solid, by

1 conventional methods such as ball-milling, calendering, stirring, or roll-milling,  
2 and then pressed into a preselected, layer-forming shape.

3 In the manufactures as presented above, the manufacture comprising  
4 a drug and a polytol are placed in contact with the displacement layer, and  
5 the two layers are surrounded with a semipermeable wall. The layering of the  
6 drug composition and the second displacement composition can be  
7 accomplished by using a conventional two-layer tablet press technique. The  
8 wall can be applied by molding, spraying or dipping the pressed shapes into  
9 wall-forming materials. Another technique that can be used for applying the  
10 wall is the air-suspension coating procedure. This procedure consists in  
11 suspending and tumbling the two layers in a current of air until the wall  
12 forming composition surrounds the layers. Manufacturing procedures are  
13 described in Modern Plastics Encyclopedia, Vol. 46, pp. 62-70 (1969); and in  
14 Pharmaceutical Sciences, by Remington, 14th Ed., pp. 1626-1979 (1970)  
15 published by Mack Publishing Co., Easton, PA. The dosage form can be  
16 manufactured by following the teaching the U. S. Patent Nos. 4,327,725;  
17 4,612,008; 4,783,337; 4,863,456; and 4,902,514.

18 Exemplary solvents suitable for manufacturing the wall, the  
19 composition layers and the dosage form include inert inorganic and organic  
20 solvents that do not adversely harm the materials, the wall, the layer, the  
21 composition and the drug. The solvents broadly include members selected  
22 from the group consisting of aqueous solvents, alcohols, ketones, esters,  
23 ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics,  
24 aromatics, heterocyclic solvents, and mixtures thereof. Typical solvents  
25 include acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol,  
26 butyl alcohol, methyl acetate, ethyl acetate, isopropyl n-butyl acetate, methyl  
27 isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol  
28 monoethyl ether, ethylene glycol monoethylacetate, methylene dichloride,  
29 ethylene dichloride, propylene dichloride, chloroform, nitroethane,  
30 nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane,

1       cyclo-octane, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme,  
2       aqueous and nonaqueous mixtures, such as acetone and water, acetone and  
3       methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and  
4       ethylene dichloride and methanol.

5

6       DETAILED DISCLOSURE OF EXAMPLES

7

8       The following examples are merely illustrative of the present invention  
9       and they should not be considered as limiting the scope of the invention in  
10      any way, as these examples and other equivalents thereof will become  
11      apparent to those versed in the art in the light of the present disclosure and  
12      the accompanying claims.

13

14       EXAMPLE 1

15       The therapeutic composition provided by the invention is prepared as  
16      follows: first, 2.4 g of oxybutynin hydrochloride, 42.6 g of mannitol, and 0.2 g  
17      of magnesium stearate are dry blended for 10 minutes in a 200 ml beaker,  
18      with mixing for 10 minutes with a stainless steel spatula. Next, the dry blend  
19      drug composition is compressed into a single layer tablet. 150 mg of the dry  
20      composition is compressed under a pressure head of two tons into a 9/32  
21      inch (7.14 mm) diameter standard round tablet to provide the composition  
22      comprising a drug and polyitol.

23

24       EXAMPLE 2

25       A dosage form adapted, designed and shaped as a delivery device is  
26      manufactured as follows: first, 2.4 g of oxybutynin hydrochloride, 42.6 g of  
27      mannitol, and 0.2 g of magnesium stearate are dry blended for 10 minutes to  
28      produce a homogenous blend. Next, 150 mg of the drug composition is  
29      compressed under a pressure head of two tons into a 9/32" (7.14 mm)  
30      diameter round tablet.

1        Next, a number of tablets are coated with a wall comprising a  
2        semipermeable polymer. The wall forming composition comprises 99%  
3        cellulose acetate having a 32.0% acetyl content, and 1% polyethylene glycol  
4        of 3350 molecular weight. The wall forming composition is dissolved in a  
5        acetone: water 88:12 (wt:wt) cosolvent to make a 5 wt % solids solution. The  
6        wall forming composition is sprayed onto the therapeutic tablets in a 24"  
7        coater.

8        Then, one 25 mil (0.635 mm) exit passageway is drilled through the  
9        semipermeable wall to connect the dry, blended drug composition with the  
10       exterior of the dosage form. The residual cosolvent is removed by drying for  
11       48 hours at 50°C and 50% humidity. Next, the dosage forms are dried for 4  
12       hours at 50 ° C to remove excess moisture. The dosage forms produced by  
13       this manufacturer provide 5 wt % oxybutynin, 94.75 wt % mannitol, and 0.25  
14       wt % magnesium stearate. The semipermeable wall comprises 99 wt %  
15       cellulose acetate comprising 32.0% acetyl content, and 1.0 wt % polyethylene  
16       of 3350 molecular weight. The dosage form comprises one exit passageway,  
17       25 mil (0.635 mm) and has an oxybutynin mean release rate of 1.29 mg/hr.

18

19

### EXAMPLE 3

20       The procedures of the above examples are followed for manufacturing  
21       a dosage form comprising a therapeutic composition weighing 154 mg and  
22       consisting of 3.25 wt % (4.92 mg) of oxybutynin hydrochloride, 89.50 wt %  
23       mannitol, 3.00 wt % hydroxypropylmethylcellulose of 9,200 molecular weight,  
24       0.25 wt % magnesium stearate, and 4.00 wt % polyvinylpyrrolidone of 40,000  
25       molecular weight. The therapeutic composition is surrounded by a wall  
26       weighing 14.3 mg and consisting of 48.8 wt % cellulose acetate comprising a  
27       32% acetyl content, 46.20 wt % cellulose acetate comprising a 39.8% acetyl  
28       content, and 5.00 wt % polyethylene glycol of 3350 molecular weight. The  
29       dosage form comprises a 30 mil passageway. Accompanying Figure 4

1 depicts the cumulative dose of oxybutynin hydrochloride released over 36  
2 hours.

3

4 **EXAMPLE 4**

5 A therapeutic composition comprising a polyitol and a drug selected  
6 from the group consisting simvastatin, sumatriptan, doxazosin, amlodipine,  
7 azithromycin, lisinopril, and finasteride is prepared by following the above  
8 examples. The therapeutic composition is enveloped with a wall comprising a  
9 semipermeable composition and an exit in the wall for delivering the drug to a  
10 patient of need of therapy at a sustained-release rate over an extended time.

11

12 **EXAMPLE 5**

13 A dosage form adapted, designed as an elementary osmotic delivery  
14 device is manufactured as follows: First, the following ingredients are mixed  
15 in a beaker: oxybutynin chloride (9.75 grams), mannitol USP (268.5 grams),  
16 hydroxypropyl methyl cellulose of 9,200 molecular weight (9.0 grams), and  
17 polyvinylpyrrolidone of 40,00 molecular weight (112.0 grams). Then, 45 ml of  
18 anyhydrous ethanol is added to the mixture while stirring with a stainless  
19 steel spatula. The wet granulation is then passed through a 20-mesh box  
20 sieve, and dried at room temperature for approximately 16 hours. The dry  
21 granulation is then passed through a 20-mesh sieve once again.

22 Next, the granulation is placed in a jar, and magnesium stearate (0.75  
23 grams) lubricant is added. This is blended for 90 seconds on a mechanical  
24 roller. Next, 154 mg of the drug granulation is compressed under a pressure  
25 head of 0.5 tons into a 9/32" (7.14 mm) diameter standard round tablet.

26 The tablets are then coated with a semipermeable wall. The wall  
27 forming composition comprises 48.8% cellulose acetate having a 32.0%  
28 acetyl content, 46.2% cellulose acetate having a 39.8 acetyl content, and 5%  
29 polyethylene glycol having a molecular weight of 3350. The wall forming  
30 composition is dissolved in methylene chloride/methanol (80:20 wt:wt)

1 cosolvent to make a 4% solids solution. The wall forming composition is  
2 sprayed onto the tablets in a 24" coated to an average weight of 14.3 mg per  
3 system.

4 Next, one 25 mil (0.635 mm) exit passageway is drilled through the  
5 semipermeable wall. The residual solvent is removed by drying for 48 hours  
6 at 45° C to 45° C. Next the osmotic dosage form are dried for 4 hours at 45° C  
7 to remove excess moisture. The dosage form produced by this manufacture  
8 provides 3.25 wt% oxybutynin chloride, 89.5% mannitol possessing a 182  
9 molecular weight, 3.0% hydroxymethylpropyl-cellulose, 4.0% polyvinyl-  
10 pyrrolidone, and 0.25% magnesium stearate. The semipermeable wall  
11 comprises 48.8 wt % cellulose acetate comprising a 32.0% acetyl content,  
12 46.2% cellulose acetate having a 39.8% acetyl content, and 5.0 wt %  
13 polyethylene glycol with a molecular weight of 3350. The dosage form has  
14 one exit passageway, 25 mil (0.635 mm), and provides a mean release rate  
15 of 0.28 mg/hr between 0 and 14 hours.

16

17 **METHOD OF PRACTICING THE INVENTION**

18

19 The invention pertains additionally to the use of the therapeutic  
20 composition, and the dosage form by providing a method for delivering a drug  
21 orally to a warm-blooded animal, including a human patient in need of  
22 therapy. The method comprises administering orally the therapeutic  
23 composition to a patient for therapy by admitting into the patient a therapeutic  
24 composition comprising a drug and a polyitol. The method comprises also  
25 admitting orally into a patient a dosage form comprising a semipermeable wall  
26 that surrounds a therapeutic composition comprising a dose of drug and a  
27 polyitol. The dosage form imbibes fluid through the semipermeable wall into  
28 the dosage form in response to the concentration gradient across the  
29 semipermeable wall. The therapeutic composition in the dosage form  
30 develops polyitol generated osmotic energy that causes the therapeutic

1 composition to be administered through an exit in the wall over a prolonged  
2 period of time up to 30 hours to provide controlled and sustained therapy.

3       In summary, it will be appreciated that the present invention  
4 contributed to the art an unobvious dosage form that possesses practical  
5 utility, can administer a drug at a dose-metered release rate per unit time.  
6 While the invention has been described and pointed out in detail with  
7 reference to operative embodiments thereof, it will be understood by those  
8 skilled in the art that various changes, modifications, substitution and  
9 omissions can be made without departing from the spirit of the invention. It is  
10 intended, therefore, that the invention embrace those equivalents within the  
11 scope of the claims which follow.